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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,597	02/19/2002	Roderic M.K. Dale	054800-5003-02	2708

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,597	DALE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,23 and 25-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,23 and 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-12-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 23, 25-31 are currently pending in the instant application. Applicants cancelled claims 4-22, 24, and 32-41 in the preliminary amendment filed 2-19-02.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 23, 25-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

4. The instant claims are drawn to acid resistant oligonucleotides targeting nucleic acid involved in PDE4 expression, having a nucleic acid backbone structure modified from that of naturally occurring nucleotide polymer, a blocking chemical modification at or near the 3'end, wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH of about .01 or 0.1 to about 10, and nuclease resistance of at least twice that of a naturally occurring polymer having the same number of nucleotides; and methods of using said acid resistant oligonucleotides.

The specification as filed does not specifically describe a representative number of species of the claimed genus of acid resistant oligonucleotides possessing the above characteristics that would allow one of ordinary skill in the art to envisage the structures of all

the members of the claimed genus. The specification as filed mentions a variety of modifications that may influence the acid stability of an oligomer, however there are no specific examples of modified oligomers that display the range of pH stability as claimed by Applicants. Furthermore, there is only one example of a specifically modified oligonucleotide mentioned in the specification as filed, OE-2a, it is a 2'-O-methyl RNA oligonucleotide, phosphodiester linked, with 5' and 3' "ends blocked" with inverted Ts (thymines?) that is targeted to the human PDE4 gene. However, the acid resistance and the pH stability of this oligonucleotide was not described, nor was there any other example given in the specification as filed that would clearly shed light on the specific modifications that would produce antisense oligonucleotides that are characterized by a pH stability of at least one hour at a pH of about 0.01 or 0.1 to about 10 and a nuclease resistance of at least twice that of a naturally occurring unmodified polymer.

According to MPEP § 2163[R-1]I.A. "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." In the instant case, Applicants provide only one example of a modified oligonucleotide comprising modifications according to the present invention, however there is no indication as to whether this oligonucleotide has a pH stability of at least one hour at a pH of about 0.01 or 0.1 to about 10 and a nuclease resistance of at least twice that of a naturally

occurring unmodified polymer. It is unclear if this one example (OE-2a) is representative of the full scope of acid resistant oligonucleotide encompassed by the claimed invention. It is apparent that further experimentation would be required to determine the structures of the full scope of compounds encompassed by the instant claims, therefore Applicants were not in possession of the full scope of compounds or methods of use recited in the instant claims.

Additionally, it is noted that claims 28-31 are drawn to methods comprising the administration of an acid resistant oligonucleotide that binds selectively to "DNA involved in phosphodiesterase 4 expression." However, DNA involved in PDE4 expression may include all allelic and polymorphic variants of genes that encode transcription factors which regulate PDE4 transcription, enhancer or silencer PDE4 transcription regulatory elements, and genes that encode RNA binding proteins that may bind and inhibit the translation of PDE4, etc. Claims 28-31 read on DNA sequences whose structures are not described in the specification. Therefore, since these sequences are not sufficiently described it is not possible for anyone of skill in the art to design the full scope of acid resistant oligonucleotides that bind selectively to all DNA sequences involved in PDE4 expression encompassed by the instant claims, with the exception of those DNA sequences encoding PDE4 as described by the specification.

Therefore, the specification does not describe the claimed compositions in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application.

5. Claims 23, and 25-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the OE-2a (SEQ ID NO: 32) oligonucleotide for topically treating dermatitis in a patient, does not reasonably provide enablement for treating

other diseases comprising the administration of any other oligonucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Although applicants were able to provide therapeutic results comprising the administration of the OE-2a oligonucleotide for the topical treatment of dermatitis and allergic rhinitis, the results observed using the OE-2a cannot be extrapolated to predict the therapeutic effectiveness of any and all oligonucleotides targeting a PDE4 mRNA. The ability of an oligonucleotide to be effective for the treatment of a disease must be determined independently. According to Crooke (1998), there are a variety of factors that influence the activity of antisense-based compounds in a cellular environment. For example, Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by factors including: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. Additionally, Crooke (1998) teaches that non-antisense effects, such as non-specific protein binding, influence various properties of oligonucleotides including cellular uptake, distribution, metabolism and excretion of said oligonucleotides. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors, which influence the behavior of antisense based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Moreover, Branch states that "[H]owever, their *(antisense molecules and ribozymes)* unpredictability confounds research applications of nucleic acid reagents."

Jen et al. (*Stem Cells,* Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[G]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[A] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (see page 315, last two paragraphs).

It is apparent from Branch, Crooke, and Jen et al. that the art of antisense base therapeutics (at the time of filing) is unpredictable and those highly skilled in the art are working towards making the antisense therapy more predictable have many obstacles to overcome. Therefore, claims to antisense based pharmaceuticals and methods of treating diseases by the

administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the behavior of antisense oligonucleotides within a cell and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3, are rejected under 35 U.S.C. 103(a) as being unpatentable over Owens et al. in view of Miller et al.

Owens et al. provide antisense DNA or antisense RNA of a gene coding for human phosphodiesterase type IVC (See col. 2, lines 61-67, and col. 3). SEQ ID NO: 34 of Owens et al. is identical to SEQ ID NO: 48 of the instant application. Furthermore, Owens et al. teach that knowledge of the nucleic acid according to the invention also provides the ability to regulate its activity in vivo by the use of antisense DNA or RNA or an analogue or fragment thereof. The

antisense DNA or RNA of Owens et al. can be produced using conventional means, by standard molecular biology techniques and/or by chemical synthesis. If desired, the antisense DNA and antisense RNA may be chemically modified so as to prevent degradation in vivo or to facilitate passage through a cell membrane, and/or a substance capable of inactivating mRNA, for example a ribozyme may be linked thereto, and the invention extends to such constructs (col. 3, lines 1-16). However, Owens et al. do not teach the synthesis of acid resistant oligonucleotides having a blocking chemical modification at or near the 3' end, nor do they teach wherein the oligonucleotide has a pH stability of at least one hour at a pH of about .01 to about 10.

Miller et al. teach oligomers modified to improve stability at acid pH, and methods of delivering such oligomers to their sites of action and to their use in formulations for oral administration or other dosage forms where acid resistance is advantageous. In one aspect of the Miller et al. invention, the acid resistant oligomers are provided wherein the nucleosidyl units have a sugar moiety which is a 2'-O-alkyl ribosyl group, the oligomer is preferably neutral, having methylphosphonate internucleosidyl linkages preferably from about 50 to 100 percent of the internucleosidyl linkages of the oligomer, the oligomer preferably comprises from about 4 to 40 nucleotides, and exhibits resistance to acid degradation (p. 2-3, 10). In particular, Miller et al. disclose a methylphosphonate oligomer having 2'-O-methyl ribosyl units that remained a 100% intact backbone at 37°C and at pH 1 (see Figure 5).

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to modify the antisense oligonucleotides of Owens et al. with the modifications of Miller et al. in order to provide acid resistant antisense oligonucleotides that are useful in formulations for oral administration and in other dosage forms where acid resistance is

advantageous. One of ordinary skill in the art would have had a reasonable expectation of success in designing such acid resistant antisense oligonucleotides targeting PDE IV (or 4) since Miller et al. teach the appropriate modifications for synthesizing an acid resistant oligonucleotide and Owens et al. discloses the sequences of multiple forms of PDE IV (or 4).

Therefore the invention as a whole is *prima facie* obvious over Owens et al. in view of Miller et al.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE